epidermolysis bullosa. *Proc Natl Acad Sci USA* 98:5193–8

Sakai N, Waterman EA, Nguyen NT *et al.* (2010) Observations of skin grafts derived from keratinocytes expressing selectively engineered mutant laminin-332 molecules. *J Invest Dermatol* 130:2147–50

Tolar J, Xia L, Riddle MJ *et al.* (2010) Induced pluripotent stem cells from individuals with recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 131: 848–56

Vailly J, Gagnoux-Palacios L, Dell'Ambra E *et al.* (1998) Corrective gene transfer of keratinocytes from patients with junctional epidermolysis bullosa restores assembly of hemidesmosomes in reconstructed epithelia. *Gene Ther* 5:1322–32

Varki R, Sadowski S, Pfendner E *et al.* (2006) Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants. *J Med Genet* 43:641–52

Wu SM, Hochedlinger K (2011) Harnessing the potential of induced pluripotent stem cells for regenerative medicine. *Nat Cell Biol* 13: 497–505

Yuen WY, Duipmans JC, Molenbuur B *et al.* (2012) Long-term follow-up of patients with Herlitz type junctional epidermolysis bullosa. *Br J Dermatol* 167:374–82

Rotating Night-Shift Work and Risk of Psoriasis in US Women

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TO THE EDITOR

Rotating night-shift work causes chronic circadian misalignment between the endogenous circadian timing system and behavioral cycles and suppresses the secretion of melatonin (James *et al.*, 2007; Scheer *et al.*, 2009). Melatonin has been found to regulate the inflammatory response and have antioxidant effects (Bonnefont-Rousselot and Collin, 2010; Ochoa *et al.*, 2011), which may thereby protect against psoriasis. One prior study showed that psoriatics had reduced plasma melatonin (Mozzanica *et al.*, 1988). A growing body of literature provides evidence linking night-shift work with various health conditions, including psoriasis comorbidities such as coronary heart disease and type 2 diabetes (Kawachi *et al.*, 1995; Gelfand *et al.*, 2006; Pan *et al.*, 2011; Li *et al.*, 2012b). However, no direct evidence of an association between night-shift work and psoriasis is available. Here, we evaluated the association between rotating night-shift work and incident risk of psoriasis in two large, prospective cohort studies, the Nurses' Health study (NHS) (1988–2008) and NHS II (1989–2005).

Details on the cohorts and ascertainment of psoriasis have been described previously (Li *et al.*, 2012b). Participants responded to clinician-diagnosed psoriasis in the 2008 (NHS) or 2005 (NHS II) questionnaires with high validity. Participants were asked about lifetime years working in rotating night shifts in the 1988 (NHS) and 1989 (NHS II) questionnaires. We classified participants into two major categories: never or ever working in rotating night shifts. The participants were further categorized by the duration of shift work: 1–2, 3–9, or ⩾10 years. Information on covariates was collected from the questionnaires biennially. From the responders to the follow-up beginning and ending questionnaires, we excluded psoriasis prevalent cases, unknown diagnosis date, and unknown status of night-shift work: 62,487 in NHS and 95,561 in NHS II remained in the analysis.

We calculated person-years of follow-up for each participant from the return date of 1988 (NHS) or 1989 (NHS II) questionnaire to the date of diagnosis of psoriasis, or the end of follow-up (June 2008 for NHS and June 2005 for NHS II), whichever came first. Time-dependent Cox proportional hazards models adjusting for 2-year time intervals were used to estimate the hazard ratios (HRs) and 95% confidence interval (CI) of developing psoriasis in night-shift workers, adjusting for age, body mass index (BMI), smoking, alcohol intake, and physical activity. The time-varying covariates were updated in the analysis. For the combined analysis, we tested the between-studies heterogeneity and estimated the overall association using meta-analysis. The institutional review board of Brigham and Women's Hospital approved this study.

In NHS, 58.8% reported ever working in rotating night shifts for at least 1 year, with 10.9% reporting ⩾10 years of rotating night-shift work. In NHS II, 61.6% reported ever working in rotating night shifts, with 4.5% working for ⩾10 years. In both cohorts, those ever working in rotating night shifts tended to have a higher BMI and were more likely to be physically active or current smokers (Table 1). Overall, 1,887 incident psoriasis cases were identified during follow-up. Compared with those who reported no night-shift work, those ever working in rotating night shifts at baseline had a significantly increased risk of psoriasis. The multivariate-adjusted HR (95% CI) was 1.26 (1.09–1.47) in NHS, 1.14 (1.01–1.28) in NHS II, and 1.19 (1.07–1.32) in combined cohorts. We evaluated the risk of psoriasis by duration of rotating night-shift work, and the multivariate-adjusted HRs (95% CIs) in the combined cohorts were 1.20 (1.07–1.34), 1.17 (1.00–1.38), and 1.23 (1.03–1.47) for 1–2, 3–9, and ⩾10 years of working in rotating night shifts, respectively (Table 2). Further adjustments by parity, postmenopausal hormone use, depression, personal history of psoriasis

Abbreviations: BMI, body mass index; CI, confidence interval; NHS II, Nurses' Health Study II

Table 1. Age-standardized baseline characteristics of the study participants by status of working rotating night shifts: Nurses' Health Study (NHS) (1988) and NHS II (1989)[1]

	NHS working rotating night shifts			NHS II working rotating night shifts		
Characteristic	**Never (*n*=25,765)**	**Ever (*n*=36,722)**	***P*-value[2]**	**Never (*n*=36,660)**	**Ever (*n*=58,901)**	***P*-value[3]**
Age[3], mean (SD), year	52.8 (6.9)	53.5 (6.9)	<0.0001	34.4 (4.7)	34.5 (4.6)	0.45
Body mass index, kg m^{-2}, mean (SD)	25.1 (4.6)	25.6 (4.8)	<0.0001	23.8 (4.8)	24.1 (5.0)	<0.0001
Current smokers (yes, %)	14.5	16.2	<0.0001	12.6	14.2	<0.0001
Alcohol intake, g d^{-1}, mean (SD)	6.0 (10.1)	6.0 (10.3)	0.43	3.0 (6.1)	3.2 (6.1)	<0.0001
Physical activity, metabolic equivalent h wk^{-1}, mean (SD)	14.9 (21.0)	16.3 (22.5)	<0.0001	19.4 (25.1)	21.6 (27.7)	<0.0001

[1]Values are means (SD) or percentages and are standardized to the age distribution of the study population.
[2]*P*-values are calculated by *t*-test or χ^2-test.
[3]Value is not age adjusted.

Table 2. Relative risk of psoriasis by baseline status of working rotating night shifts: Nurses' Health Study (1988–2008) and Nurses' Health Study II (1989–2005)

	Cases	**Person-years**	**Age-adjusted HR (95% CI)**	**Multivariate-adjusted HR[1] (95% CI)**
Nurses' Health Study	743	1,237,934		
Never	258	510,681	1.00	1.00
Ever	485	727,253	1.32 (1.13–1.53)	1.26 (1.09–1.47)
1–2 Years	193	307,126	1.24 (1.03–1.50)	1.24 (1.03–1.49)
3–9 Years	195	285,560	1.35 (1.12–1.62)	1.28 (1.07–1.55)
⩾10 Years	97	134,567	1.41 (1.12–1.79)	1.29 (1.02–1.64)
P-value for trend			0.0009	0.01
Nurses' Health Study II	1,144	1,483,567		
Never	397	569,814	1.00	1.00
Ever	747	913,753	1.17 (1.04–1.32)	1.14 (1.01–1.28)
1–2 Years	357	432,809	1.18 (1.02–1.36)	1.18 (1.02–1.36)
3–9 Years	328	414,435	1.14 (0.98–1.32)	1.09 (0.94–1.26)
⩾10 Years	62	66,509	1.30 (0.99–1.70)	1.14 (0.87–1.50)
P-value for trend			0.067	0.42
Nurses' Health Study/Nurses' Health Study II				
Never	655	1,080,495	1.00	1.00
Ever	1,232	1,641,006	1.23 (1.10–1.38)	1.19 (1.07–1.32)
1–2 Years	550	739,935	1.20 (1.07–1.35)	1.20 (1.07–1.34)
3–9 Years	523	699,995	1.23 (1.04–1.45)	1.17 (1.00–1.38)
⩾10 Years	159	201,076	1.29 (1.08–1.53)	1.23 (1.03–1.47)
P-value for trend			0.001	0.049

Abbreviations: CI, confidence interval; HR, hazard ratio.
[1]Adjusted for age (in continuous variable), body mass index (<21, 21–22.9, 23–24.9, 25–26.9, 27.0–29.9, 30.0–32.9, 33–34.9, ⩾35 kg m^{-2}), smoking (never, past, current with 1–14, 15–24, ⩾25 cigarettes per day), alcohol intake (no, <4.9, 5.0–9.9, or ⩾10.0 g d^{-1}), and physical activity (<3, 3.0–8.9, 9.0–17.9, 18.0–26.9, or ⩾27.0 metabolic equivalent h wk^{-1}). The covariates were time varying and updated in the analysis.

comorbidities, as well as sleep and snore frequency (only for NHS), did not appreciably change the results.

Night-shift work has been associated with an increased risk of psoriasis comorbidities, with the major underlying mechanism postulated to be exposure to light during the night, leading to disrupted circadian rhythm and decreased melatonin synthesis (Scheer *et al.*, 2009). Melatonin also has potent antioxidant properties (Bonnefont-Rousselot and Collin, 2010; Ochoa *et al.*, 2011). Night-shift workers may therefore have increased risk for

psoriasis because of the diminished ability of the pineal gland to produce melatonin. Another potential explanation may point to vitamin D deficiencies in night workers, with a prior study demonstrating significantly lower vitamin D levels associated with night work (Ward *et al.*, 2011), whereas vitamin D derivatives are part of standard treatment in psoriasis as well as psoriatic arthritis (Bailey *et al.*, 2012). Because we were unable to control for exposure to sunlight or vitamin D levels, confounding by vitamin D cannot be ruled out.

An increased risk of psoriasis associated with working in shifts may also be partly due to other behavioral risk factors. Those working with a rotating night shift schedule tended to have a higher BMI and were more likely to smoke. Results remained significant, however, after adjusting for these two major psoriasis risk factors (Setty *et al.*, 2007; Li *et al.*, 2012a). Given the strong associations among obesity, weight gain, and psoriasis (Setty *et al.*, 2007), a healthy diet could have beneficial effects on psoriasis. The temporal distribution of eating may be affected by shift work (Lowden *et al.*, 2010), but one recent study did not support differences in total energy intake and dietary score between daytime and shift workers (Pan *et al.*, 2011). We did not observe marked changes in the effect estimation after additional adjustments to the sensitivity analysis. Nevertheless, an observational study cannot rule out the role of other unfavorable changes in health behaviors among rotating night-shift workers in explaining the observed association.

Approximately 8.6 million Americans work in shifts. Our prospective analysis identified an association between rotating night-shift work and an increased risk of psoriasis, indicating a long-term effect of working night shifts, which may help increase the awareness of psoriasis risk among people who work in rotating shifts. Our participants are overwhelmingly white female nurses; therefore, any extrapolation to other populations should be made with caution.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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REFERENCES

Bailey EE, Ference EH, Alikhan A *et al.* (2012) Combination treatments for psoriasis: a systematic review and meta-analysis. *Arch Dermatol* 148:511–22

Bonnefont-Rousselot D, Collin F (2010) Melatonin: action as antioxidant and potential applications in human disease and aging. *Toxicology* 278:55–67

Gelfand JM, Neimann AL, Shin DB *et al.* (2006) Risk of myocardial infarction in patients with psoriasis. *JAMA* 296:1735–41

James FO, Cermakian N, Boivin DB (2007) Circadian rhythms of melatonin, cortisol, and clock gene expression during simulated night shift work. *Sleep* 30:1427–36

Kawachi I, Colditz GA, Stampfer MJ *et al.* (1995) Prospective study of shift work and risk of coronary heart disease in women. *Circulation* 92:3178–82

Li W, Han J, Choi HK *et al.* (2012a) Smoking and risk of incident psoriasis among women and men in the United States: a combined analysis. *Am J Epidemiol* 175:402–13

Li W, Han J, Hu FB *et al.* (2012b) Psoriasis and risk of type 2 diabetes among women and men in the United States: a population-based cohort study. *J Invest Dermatol* 132:291–8

Lowden A, Moreno C, Holmback U *et al.* (2010) Eating and shift work—effects on habits, metabolism and performance. *Scand J Work Environ Health* 36:150–62

Mozzanica N, Tadini G, Radaelli A *et al.* (1988) Plasma melatonin levels in psoriasis. *Acta Derm Venereol* 68:312–6

Ochoa JJ, Diaz-Castro J, Kajarabille N *et al.* (2011) Melatonin supplementation ameliorates oxidative stress and inflammatory signaling induced by strenuous exercise in adult human males. *J Pineal Res* 51:373–80

Pan A, Schernhammer ES, Sun Q *et al.* (2011) Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med* 8:e1001141

Scheer FA, Hilton MF, Mantzoros CS *et al.* (2009) Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci USA* 106:4453–8

Setty AR, Curhan G, Choi HK (2007) Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. *Arch Intern Med* 167:1670–5

Ward M, Berry DJ, Power C *et al.* (2011) Working patterns and vitamin D status in mid-life: a cross-sectional study of the 1958 British birth cohort. *Occup Environ Med* 68:902–7

Modeling Pattern Formation in Skin Diseases by a Cellular Automaton

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TO THE EDITOR

Visual perception has an important role for dermatologists in making a diagnosis; therefore, they invest much effort in providing accurate descriptions of clinical manifestations. The sophisticated use of a metaphoric language with words such as annular, discoid, polycyclic, circinate, garland-like, and others indicates the complexity of the challenge. Although morphology is an essential marker for diagnosis and therapeutic response, the mechanisms underlying the formation of these difficult-to-describe cutaneous patterns are unknown. In the presented approach, we tested whether typical skin diseases and their dynamic course can be